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Bristol-Myers Squibb Company

2004 DEC 29 P5:51

**December 28, 2004**

**Dockets Management Branch**
**Food and Drug Administration, HFA-305**
**5630 Fishers Lane, Room 1061**
**Rockville, MD 20852**

**Re: Docket No. 2004D-0459; Draft Guidance, Draft Guidance for Industry on Pharmacokinetics in Pregnancy-Study Design, Data Analyses, and Impact on Dosing and Labeling, 69 Federal Register 63402** ***(November 1, 2004).***

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the above draft guidance. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the draft guidance. Our comments are set forth below.

**Summary of BMS Comments on Proposal**

We commend the U.S. FDA for addressing the need for better prescribing information for pregnant women needing medication during their pregnancy. We appreciate that this patient population is not frequently studied during drug development because of concern over potential or unknown risks to the developing fetus. We are also aware that despite the lack of efficacy and safety data in pregnant patients, many approved drugs will be used to treat acute and chronic conditions during pregnancy. Conversely, needed therapy may be withheld or discontinued because of medication concerns in pregnancy. For drugs without a significant teratogenic or other pregnancy-related risk, additional information on the safe use of a medication (including pharmacokinetic and/or pharmacodynamic data) may allow for use of a drug in pregnant women.

We agree with FDA that any PK studies performed with pregnant subjects must conform to regulations (45 CFR Subpart B 46.204) which require that "preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means." We also agree with FDA that PK studies, if needed, should occur in the post-marketing period as it becomes evident that the medication is being used to treat significant medical conditions in pregnant women.

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Consideration to perform PK studies in pregnant women during a Phase 3 development program should be restricted to an unmet medical need for therapy in this specific patient population.

In addition, we strongly agree that all of these studies be limited to pregnant women who need the drug for therapeutic reasons as determined by their physicians, and that the drug studied has an acceptable risk/benefit ratio and is a reasonable alternative to other available therapies. However, we have significant reservations about performing these studies in "normal pregnant volunteers" and do not think that it would be ethically acceptable to include them even in single-dose pharmacokinetic studies. In addition to these general comments, we would also like to provide comments on specific sections of the Guidance:

## II. Background

Lines 76-78. The term "majority" may be inappropriate. Several vertical transmission studies have been performed with anti-HIV agents where drug concentrations have been determined in maternal, fetal, and/or newborn blood.

Lines 91-100. Potential pregnancy-related changes in receptor sensitivity to drug have not been addressed.

It should be noted that well-designed Phase 3 studies that incorporate population PK may provide insight on how altered physiological states may impact the PK of a drug and its metabolites, and thus may be helpful for predicting doses in pregnant women. For example, hepatic and renal impairment studies can provide insight on the effects of altered blood flow on the pharmacokinetic behavior of a drug or metabolite.

## III. Deciding Whether to Conduct a Pharmacokinetic Study in Pregnant Women

The guidance mentions utilizing the results of preclinical reproductive toxicity studies to assess the risk associated with performing PK studies in pregnant women with a given drug. It is recommended that consideration be given to comparing existing preclinical data in pregnant (reproductive toxicology studies) versus nonpregnant (toxicology studies) animals (e.g., rats and other species when possible) in assessing the potential for divergent drug exposures as a function of pregnancy as well as across species. Although the ICH guidelines do not require TK studies to be performed in pregnant animals in reproductive toxicity studies, it is nonetheless a fairly routine component of the preclinical study package for many drugs and should therefore be easily available for reference. Depending upon the outcome of such a comparison, the need for recommended PK studies in pregnant women may be modulated or made more apparent.

Other preclinical data may also help in determining the need for a separate PK assessment in pregnant women. State-of-the-art basic research is now often able to supplement, bolster or possibly eliminate experimental plans based on knowledge of how a molecule performs and the physiological context of the clinical experience. For example, if the kinetic behavior of a drug is largely controlled by renal blood flow, it may be possible to better design a clinical plan or eliminate certain types of human studies. Likewise, extra work may be required if additional variables are identified (e.g. accumulation of a potentially toxic metabolite in the fetus).

Line 126. The guidance mentions utilizing results of preclinical toxicity studies to assess risk associated with performing PK/PD study in pregnant women. We recommend that consideration be given to comparing the metabolic profile of a drug between the species used in reproductive toxicology studies and humans. If unique metabolites exist in humans, then it would be prudent to include the metabolite in the reproductive toxicity studies to minimize risk. Regarding exposure assessments, the guidance should encourage the use of biologically-based computational models (eg, physiologically-based pharmacokinetic modeling) to predict dosimetry in the developing embryo, fetus, and newborn.

Lines 138-140. It seems that only population PK in conjunction with sparse sampling and Bayesian approaches may be suitable in these situations since a traditional or 'frequentist' design may be less appealing to these subjects.

IV. **Study Design** - FDA suggests two possible study designs.

**A. Longitudinal Design** - The first proposed study method involves a longitudinal design for patients receiving a medication throughout pregnancy. This design allows each woman to serve as her own control with a postpartum study point acting as the baseline non-pregnant assessment. This design will be useful for conditions requiring continuous treatment throughout pregnancy but may be logistically difficult to study and/or interpret for medications taken intermittently or for limited periods during pregnancy. In this case, non-pregnant patients with the same condition and treatment requirement could serve as the control group.

Lines 186 - 187. Longitudinal study designs which incorporate intensive blood and urine PK sampling may make study enrollment difficult.

**B. Population PK Design** - As FDA stated, the population PK study design may be a preliminary approach to understanding drug pharmacokinetics in the pregnant population acknowledging that multiple maternal covariates are likely to be present in this type of study including variability in maternal age, race, weeks of gestation, concomitant medications, etc. This design may provide snapshot information that can compare PK data between pregnant and non-pregnant patients with the same medical conditions. We would suggest, however, that

study sites enrolling pregnant patients into this type of study, have expertise in obstetrics so that safety concerns specific to the pregnant patient are recognized and appropriately evaluated.

Due to the multiple variables introduced by pregnancy as mentioned above, the population PK approach in this setting will necessitate very large subject numbers at each gestational phase to develop an objective, robust and predictive model. It is anticipated that enrollment will be difficult and these studies will take a long time to complete. Sites that typically conduct Phase 3 studies may experience difficulty in appropriate PK sample collection, handling, and storage procedures.

## V. Other Design Considerations

**A. Study Participants** - We agree with FDA that study participants should be representative of a typical patient population for the anticipated use of drug but are unclear as to the number of subjects and the variables (eg. age, weight, renal function, ethnicity, etc.) that need to be represented in a PK study so that the data can be generalizable to diverse pregnant patients. While inclusion and exclusion criteria can control patient characteristics for study enrollment, variables may not remain comparable among study participants throughout the trial. For example, weight gain may vary significantly in otherwise normal pregnant women or some participants may develop unexpected medical conditions (eg. hypertension, gestational diabetes, etc.) later in the course of the study.

**B. Postpartum Assessments**

Lines 285-287. For longitudinal study designs, it should be noted that a woman's body weight may not return to baseline levels during the postpartum period, thus making it difficult in some cases to assess the effects of pregnancy on the PK of a drug.

Lines 292-295. PK linearity may differ in the pregnant and baseline states. Thus, comparison of single-dose PK in the postpartum period to multiple-dose PK during pregnancy may be difficult.

Lines 297-299. What are appropriate safety precautions for breast-fed infants? It would be prudent to conduct a human lactation study prior to allowing women who participate in these studies to breast-feed their infants.

**E. Sample Collection and Analysis:**

The bioanalysis of bound and unbound fractions of drug and metabolite in plasma and measurements in urine will be resource intensive. Therefore, the rationale for measuring both the bound and the unbound fractions for drugs that exhibit $\geq 80\%$ plasma protein binding should be provided in the guidance.

**F. Studies with No Intended Therapeutic Benefit** - We strongly disagree with FDA's suggestion that drugs be studied in pregnant subjects where there is no intended direct therapeutic benefit. Since it is not possible to know or foresee all risks associated with drug treatment during pregnancy, it is difficult to conclude that risks to the mother or fetus are minimal when administering an agent to subjects not needing that therapy. Rather, we suggest that if appropriate, studies target different subpopulations of pregnant women who need the medication in order to provide a broader PK/PD drug profile in pregnancy.

## VI. Data Analysis

### A. Parameter Estimation

The guidance recommends that parameters such as CLT, CL/F, CL, Vz/F or Vss/F, and t1/2 be measured, but does not discuss how these parameters would be used for making dosing recommendations.

### B. Development of Dosing Recommendations

In general, PK/PD studies in pregnant women will be too small to provide specific dosing recommendations for the product label given the potential for wide variability of PK within each trimester and possible confounding medical conditions not evaluated in limited PK studies.

Lines 416-420. Dosing recommendations based on unbound plasma concentrations may not hold if receptor sensitivity to drug changes during pregnant state. For drugs that exhibit poor exposure-response relationships, PK-based dosage adjustment would be difficult.

Lines 431-434. The statistical analysis of data for the studies recommended in this guidance have not been adequately addressed. It is not clear whether no effect boundaries of 80-125% will be an adequate standard to measure the changes. It seems to have been used as a default. Also, the reference to having a predefined no effect criteria is not elaborated, especially which criteria need to be considered prior to defining a no effect boundary. Although specific no effect boundaries could be chosen before the trial, the usefulness and acceptability of such criteria is unknown at this time and needs to be clearly stated.

## VII. Labeling

We are pleased to see that FDA is recommending "that labeling reflect the data from PK/PD studies in pregnancy and ... If the PK/PD is altered during pregnancy, the appropriate description of such .... should be stated in labeling." We agree with the Agency, that the results of these studies should be described in the Clinical Pharmacology Section of the product label. Additionally, we would also recommend inclusion of pregnancy outcome information from these studies

in the product label. While outcome data will be limited because of the size of most PK studies, they will begin to provide context around the PK/PD data.

**B. Precautions/Pregnancy**

There is, however, one other labeling issue raised by this Guidance for which clarification from the Agency is needed. Specifically, providing dosing information for use in pregnancy (as specified in the Guidance) may be contradictory to the pregnancy precautions or warnings implied in a Pregnancy Category (C, D or X) assigned to the drug. These broad categories imply that risks associated with drug use in human pregnancy are unknown or suspected. Pregnancy Categories are assigned at the time of marketing approval and are based primarily on animal findings. In addition, based on review of product labels, the application of these Category designations does not always appear to reflect consistent standards. We, therefore, recommend that the current Pregnancy Label Categories be revised to better characterize human pregnancy risks for a specific compound so that any dosing recommendations on the use of the drug in pregnancy will not result in prescribing confusion.

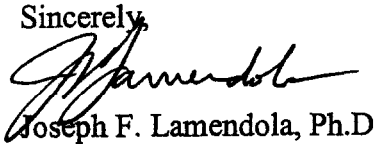
**C. Dosage and Administration**

As previously stated in our comments on **Section VI.B. Development of Dosing Recommendations**, specific dosing recommendations and dosing adjustment for use in pregnancy will be difficult and perhaps inappropriate to provide. There may be wide variability of PK/PD within each trimester and the postpartum period which will not be fully reflected in sampling from limited PK study periods. In addition, confounding medical conditions and poor exposure-response relationships may alter drug effect and make dosing recommendations difficult.

Although limited PK/PD data obtained from other subpopulations (e.g., elderly, renally-impaired, etc.) are used for dosing recommendations for these subgroups, these PK data are assessed within the context of efficacy and safety information from Phase 3 studies which often include subjects from these subpopulations. However, risk/benefit information based on safety and efficacy from large trials will generally not be available for pregnant patients. Therefore, instead of providing a dosing adjustment regimen for pregnancy, we recommend that the prescriber be referred to the Clinical Pharmacology section of the label. Review of available PK/PD results in pregnant women will allow prescribers to determine the need for dose adjustment in individual patients.

Bristol-Myer Squibb appreciates the opportunity to comment on this Draft Guidance on Pharmacokinetics in Pregnancy. We hope that our comments are helpful to the Agency and will be considered as the Guidance is implemented. Please feel free to contact us if we can be of further assistance in this matter.

Sincerely,



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